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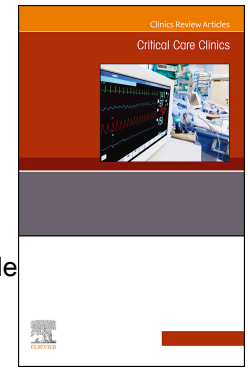

TAcute Neurological complications of COVID19 and Post-Acute Sequalae of COVID19 (PASC)

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Title Page:

- Article Title: **Acute Neurological complications of COVID19 and Post-Acute Sequalae of COVID19 (PASC)**

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- Key Words (4-8 words to direct and optimize search results): neurological complications, Long-COVID, cerebrovascular complications, neuro-COVID
- Key Points (3-5 bulleted sentences indicating the main takeaways/defining elements of the article)
    - Neurological complications of COVID19 are common. They can occur in patients with mild to severe COVID19.
    - Cerebrovascular complications such as acute ischemic stroke are seen in about 1.5% of all COVID19 patients, while cerebral sinus venous thrombosis (CSVT) is rare and intracerebral hemorrhage can occur as a consequence of therapeutic anticoagulation or due to hemorrhagic transformation of acute ischemic stroke.

Stroke systems of care must be adapted to provide the same high quality care for COVID19 patients to uphold time is brain by providing rapid access to testing and personal protective equipment (PPE).

- Coma and prolonged disorders of consciousness maybe seen in COVID19 patients either as a consequence of viral infection, prolonged use of sedative drips and delayed metabolism of these medications due to hepato-renal dysfunction. Delirium is common in COVID19. Compliance with the ICU liberation bundle or the A2F bundle was lower than during the first and second waves of COVID19 and lack of family visitation may have been an important contributor to increased incidence of delirium.
- Neurological complications in PASC range from persistent fatigue, headaches, brain fog, depression, anxiety, postural orthostatic tachycardia even in patients with mild disease to an overlap with post intensive care syndrome (PICS) in ICU survivors highlighting the need for long term follow-up.

- Synopsis (100 words or less): Neurological complications can be seen in mild to severe COVID19 with a higher risk on patients with severe COVID19. These can occur as a direct consequence of viral infection or consequences of treatments. The spectrum can range from non-life threatening such as headache, fatigue, malaise, anosmia, dysgeusia to life threatening complications such as stroke, encephalitis, coma, Guillain barre syndrome among others. A high index of suspicion can aid in early recognition and treatment. Outcomes depend on severity of underlying COVID19, patient age, comorbidities and severity of the complication. PASC can range from fatigue, headache, dysosmia, brain fog, anxiety, depression to an overlap with post-intensive care syndrome (PICS).

Acute Neurological complications of COVID19 and PASC

340 million people have suffered from the novel coronavirus, SARS-CoV2 (COVID19) across the world at the time of publication and 5.57 million deaths have occurred since the beginning of the pandemic. [1] COVID19 is a multi-system viral sepsis syndrome that can affect different organ systems with symptoms ranging from mild to life threatening. [2] Neurological complications are commonly described, and may occur as direct or indirect consequences of the viral infection, complications of treatment or, in some cases be incidental associations. These insults do not just occur in the acute phases with ongoing sequelae occurring and/or persisting for weeks to months after the initial infection, often as part of a syndrome known as post-acute sequalae of COVID19 (PASC) or long-COVID.[3–8] Critically ill patients have a higher likelihood of neurological complications than patients with mild COVID19. [3,4]

The recognition and diagnosis of these neurological complications is challenging, particularly in the context of overstrained medical systems, where an under-recognition or delays in diagnosis of neurological complications may contribute to poor outcomes. [5]

In this review we will highlight acute neurological complications of COVID19 as well as neurological manifestations of PASC.

In the first section of this review, we will discuss overall epidemiology, pathophysiology and risk factors for neurological manifestations followed by a discussion of specific neurological manifestations.

Epidemiology

The risk of neurological manifestations increases with hospitalization and higher severity of COVID-19 infection, although even patients with mild initial disease may have neurological sequelae. These include non-life threatening but debilitating symptoms ranging from anosmia, dysgeusia, fatigue, malaise, headaches to stroke, encephalitis, Guillain barre syndrome (GBS) among others. ***(Table 1)***

Our understanding of the neurological complications of COVID19 comes mainly from observational studies. ***Table 1*** summarizes neurological complications described in some of the larger cohort studies of hospitalized patients. In a systematic review and meta-analysis (n=13,480 patients and a third of these patients with severe COVID19), the most common neurological manifestations were myalgia (22%), dysgeusia (20%), anosmia (18%) headache (12%), dizziness (11%), encephalopathy (9.4%), and stroke (2.5%). Myalgia, elevated CK and LDH, and acute stroke were significantly more common in severe cases. [6,7]

Risk factors for acute neurpsychiatric complications and PASC

Older patients, multiple comorbidities, Hispanic, south Asian, black and mixed ethnicity, and patients with pre-existing neurological disorders have a higher risk of developing neurological complications of acute COVID19. Additional risk factors for PASC include age>40 years, white ethnicity, and female sex.[8] A systematic review identified the following risk for neuropsychiatric consequences of PASC.[9]

- For Depression and/Anxiety (seen in 20-40% of survivors): Women, those with infected family members, post-infectious physical symptoms, severe infection, elevated inflammatory markers, prior psychiatric diagnoses
- For Post-Traumatic Stress Disorder (PTSD) (20-30% of survivors): Women, younger age, critically ill, past psychiatric history, obesity, DM-II, autoimmune disorders
- For Cognitive issues such as memory loss, concentration difficulties, difficulties with multi-tasking, processing speed (20-30% of survivors): delirium, older age

Pathophysiology *(Figure 1 and Table 2)*

COVID19 can be thought of as having the following phases which includes an early viremic phase during which patients may remain asymptomatic for the first 48-72 hours followed by a prothrombotic, inflammatory phase, followed by an immune dysregulatory state. [10]

The COVID19 spike protein attaches to ACE2 receptor on various organs and activates an inflammatory cascade. It also attaches to the ACE2 receptor on endothelium and activates a prothrombotic state. [11] By binding to ACE2, the SARS-CoV2 virus may damage vascular endothelial cells by inhibiting mitochondrial function and endothelial nitric oxide synthetase activity leading to secondary cardio- and cerebrovascular effects. [12] It is possible that since the density and concentration of ACE2 receptors is limited in the central nervous system, direct viral invasion maybe a rare phenomenon. Consistent with this, viral particles have been identified very rarely in the brain in autopsy studies. Whether this is a consequence of low viral invasion or that by the time these patients died they had progressed from the early viremic to the inflammatory or pro-thrombotic state is not known.[7,13,14]

Inflammation: In autopsy series, microglial activation, microglial nodules and neuronophagia, was observed in majority of the brains. They were thought to not result from direct viral infection of brain parenchyma, but more likely from systemic inflammation, perhaps with synergistic contribution from hypoxia/ischemia. [7,13]
A postmortem study (n=43) found that neuropathological changes in patients with COVID-19 seem to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding. There was no evidence for central nervous system (CNS) damage directly caused by SARS-CoV-2.[14] Inflammation around blood vessels but not viral particles in a study that included n=8 post mortem samples suggests that COVID19 is associated with endotheliopathy and microvascular injury.[15]
Patients with coma or prolonged disorders of consciousness (DOC) may have a higher systemic inflammatory burden as compared to patients who do not have coma or DOC. [16]

Prothrombotic: COVID19 is thought to be an endotheliopathy and triggers a prothrombotic state. Of note, COVID19 ARDS patients had a higher level of various pro-thrombotic factors and thrombotic events, as compared to non-COVID19 patients.[17]

*Treatment effect*s: Severely ill COVID19 patients are at a high risk of encephalopathy, and Intensive Care Acquired Weakness (ICUAW). These neurological consequences were much higher than expected in these patients and likely explained by the prolonged needs for sedation, immobilization, and social isolation, increasing the risk of delirium and post-intensive care syndrome (PICS). While some of these factors may have been related to the severity of the underlying illness, others were likely due to the decreased compliance with the A2F bundle due to concerns for staff safety, shortage of personal protective equipment (PPE), medications, and limitations of family visitation. [18,19]

Spectrum of Neurological complications:

Neurological complications can be broadly categorized under cerebrovascular disease, CNS inflammatory disease, demyelinating disease, encephalopathy, peripheral neuropathy, taste/smell disorders, and other. [20]

Figure 2 describes a few potential ways of classifying neurological complications of COVID19.

Neurodiagnostic studies, neuromonitoring:

Early diagnosis of neurological complications in COVID19 patients will rely on focused bedside neurological examinations. Such focused clinical examinations can then guide a judicious utilization of imaging and electrophysiological studies. However, the pandemic has posed specific challenges in this clinical neuromonitoring with a reduction in both frequency of clinical exams, and compliance of bundles of care which include choice and depth of sedation and choice of pain control when patient numbers are high.

Imaging findings: Critically ill patients with COVID19 may not be stable hemodynamically or from a ventilation/oxygenation perspective to tolerate lying flat for several minutes in an MRI scanner. Performing CT scans in such patients suspected of having neurological complications may be the first step in diagnosis. Given the risk of cerebrovascular complications in these patients, it may pertinent to perform vessel imaging for the arterial and venous systems at the same time as CT or MRI session.

Common imaging findings described in patients with severe COVID19 have included leukoencephalopathy, ischemia/infarction with patterns of large vessel occlusion, leptomeningeal enhancement, encephalitis, hemorrhage in locations not typical for hypertension (lobar and/or cortical; which raises the question of whether it is secondary to anticoagulation), and perfusion abnormalities.[21] Another key finding in patients with coma/DOC have been microhemorrhages.[22]In another case series, 25/115 hospitalized patients with COVID19 had cerebral microbleeds documented on MRI, often with concomitant leukoencephalopathy. These were most common in patients with more severe respiratory illness. [23]

Other findings have included findings typical for posterior reversible encephalopathy syndrome (PRES), hypoxic ischemic encephalopathy (HIE). [24]
In a retrospective multicenter study (n=64); MRI abnormalities have included leptomeningeal enhancement in 17 percent and encephalitis in 13 percent; 46 percent of MRI studies were normal. [25]

CSF studies and biomarkers: Pleocytosis is usually not seen in CSF of COVID19 patients. Studies have demonstrated that CSF findings could range from being inflammatory to the only abnormality being an elevated protein. In a case-control study that included n=18 CSF samples from COVID19 patients, the authors described an absence of pleocytosis as well as an absence of increased pro-inflammatory markers or cytokines (IL-6, ferritin, or D-dimer). They also found that in non-COVID19 stroke patients and COVID19 stroke patients there was a similar increase in pro-inflammatory cytokines (IL-6, TNFα, IL-12p70). [26]

In a small case series of patients with moderate to severe COVID 19**,** an unusual pattern of marked CSF inflammation in which soluble markers of neuroinflammation (neopterin, β_2-microglobulin, and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein [NfL] being increased. However, white cell response and other immunologic features typical of CNS viral infections were absent.[27] In COVID19 patients with neurological manifestations, CSF pleocytosis was found to be associated with para- or post-infectious encephalitis and polyradiculitis. Elevations in anti-GD1b and anti-Caspr2 autoantibodies[28] and myelin associated glycoprotein [29] may be seen raising the possibility of SARS-CoV-2-induced secondary autoimmunity.

Serum biomarkers: Serum markers of brain injury including neurofilament light (NFL), Glial Fibrillary Acidic Protein (GFAP) and total Tau have been found to be increased in a severity-dependent manner in hospitalized patients, with elevations persisting at 4 month follow-up.[29] In these patients elevations in NFL and GFAP were associated with elevations of pro-inflammatory cytokines, as well as autoantibodies. Another case-control study that included plasma samples from n=57 patients at < 48 h of COVID-19 hospitalization, and 20 matched controls investigated levels of six brain injury molecules (BIMs), two Endothelial injury molecule (EIMs), and chemokines/cytokines. Three BIMs: MAP2, NSE and S100B, two

EIMs: sICAM1 and sVCAM1 and seven chemokines and cytokines: IL10, sCD40L, IP10, IL1Ra, MCP1 and TNFα were significantly ($p < 0.05$) elevated in the COVID-19 cohort compared to controls. [30]

In summary, pleocytosis is not seen in CSF of COVID19 patients with encephalopathy but protein levels can be elevated with oligoclonal bands. Elevated plasma and CSF levels of cytokines, GFAP and NFL in COVID-19 are thought to reflect a proinflammatory systemic and brain response that involves microglial activation and subsequent neuronal damage. [27] Further evidence for inflammatory mechanisms comes from imaging findings, which showed meningeal enhancement and diffuse white matter abnormalities as well as microhemorrhages. [13] It should be noted that several of these biomarkers are not being measured routinely as part of clinical care, and further understanding of when, how high and the meaning of elevations is required before use in clinical practice

Non-Life threatening but potentially distressing symptoms:

Anosmia/dysgeusia: A meta-analysis of 83 studies involving more than 27,000 patients, reported that olfactory dysfunction occurs in 48 percent of cases. [31] Olfactory bulb involvement was described on post mortem brain MRI earlier in the pandemic.[32] Most patients recover from anosmia and dysgeusia.[33, 34,35] Whether this high incidence of anosmia will be seen in patients with other COVID-19 variants remains to be seen.

Headache: Headache is a common symptom of COVID19. A meta-analysis that included n=3598 patients showed that headache was present in 11-14% of patients infected with COVID-19. [36]Earlier studies from China reported a lower incidence of headache at about 6.5-8.[37,38,39] In a cohort study of n=47 COVID19 patients, 64% had headaches. Bilateral headache localization was reported by 94% of patients, headache severity was determined as severe in 53%, and constant headaches with median period 15 days occurred in 15% of cases. [40]

Life Threatening Neurological Complications:

Stroke: There have been several cohort studies and meta-analyses describing the risk of stroke and outcomes in COVID19 patients. Prior to the COVID19 pandemic, it was already known that sepsis and related inflammation can trigger strokes. [41,42]

In one of the earlier reports of stroke in COVID19, that included n=108,571 patients with COVID-19, acute stroke occurred in 1.4% (95%CI: 1.0-1.9). The authors compared the risk of stroke in COVID19 patients versus those with influenza and concluded that more COVID19 patients suffer from stroke as compared to patients with influenza (0.9%). [43]

The first cases of large vessel occlusion were described in young, asymptomatic or mild COVID19 cases. Subsequent studies have shown that the average age of COVID19 patients with stroke maybe slightly lower than the average age in non-COVID19 stroke patients but stroke is not as common in young patients (<50 years of age). Also, COVID19 stroke patients tend to have a higher comorbidity burden.[44,45,46] Mechanisms of stroke can vary from thromboembolic, large artery atherosclerosis, COVID19 associated myocarditis & arrhythmias, cryptogenic.[47,48] In a review that included n=46 studies with 129, 491 patients, COVID19 stroke patients were younger, tend to be males, and have an increased stroke severity, compared with stroke patients in the pre-pandemic period. The authors found no difference in rates of intravenous thrombolysis but found that COVID19 patients were more likely to undergo thrombectomy[49,50] Stroke systems of care had to be adapted to COVID19 related staff safety, PPE, staff shortages. The AHA released a statement to provide guidance to health systems to provide expeditious access to thrombectomy.[50]

Mortality in patients with stroke and COVID19 is higher than non-COVD19 patients with a similar stroke burden.[49] A multicenter study from n=31 centers in the United States that included n=230 stroke patients found that only 33% of them were younger than 60 years of age. 50% (102/203) of the patients had poor outcomes with an observed mortality rate of 38.8% (35/219). [51] The in-hospital mortality rate for COVID19 stroke patients was about 38.1% and for ICH 58.3%. [51]

Good outcome has been reported for patients who develop malignant cerebral edema concurrent with COVID-19 and so infection should not be used to exclude patients from this potentially life-saving surgery. [52]

Hemorrhagic stroke:
Intracerebral Hemorrhage (ICH): ICH is less common than ischemic stroke after COVID-19 comprising approximately 20% of strokes, and its incidence ranges from 0.2 to 0.86 percent.[53,54] This rate is higher than the worldwide incidence of ICH which is 24.6/100,000 person-years or 0.02% per person-year.[55] In COVID19 patients with stroke, less than 20% have intracerebral hemorrhage (ICH). [56]The pooled incidence of ICH in a systematic review was 0.7% in COVID19 patients that included n=23 studies and n=148 COVID19 ICH patients.[57]

In a study that analyzed data from Vizient Clinical Data Base comparing n=559 ICH-COVID19 patients and 23,378 non-COVID19 ICH controls from 194 hospitals; COVID19 ICH patients had a longer hospital stay (21.6 vs. 10.5 days), a longer intensive-care stay (16.5 vs. 6.0 days), and a higher in-hospital death rate (46.5% vs. 18.0%). COVID19 patients with ICH or subarachnoid hemorrhage (SAH) were more likely to be a racial or ethnic minority, diabetic, and obese and to have higher rates of death and longer hospital length of stay when compared with controls.[58] A patient level pooled meta-analysis that included n=139 ICH patients with COVID-19, the authors found that these the ICH in these patients had different characteristics compared to ICH not associated with COVID-19, including frequent lobar location (67%) and multifocality (36%), a high rate of anticoagulation, and high mortality. [59] In a systematic review, [60]older age, non-Caucasian race, respiratory failure requiring mechanical ventilation, and therapeutic anticoagulation were identified as risk factors for ICH. [61]

SAH: In a study where the authors analyzed data from the Vizient database comparing COVID19 SAH cases versus non-COVID19 SAH controls, there were 212 SAH-COVID patients and 5,029 controls from 119 hospitals. The hospital (26.9 vs. 13.4 days) and intensive-care (21.9 vs. 9.6 days) length of stays and in-hospital death rate (42.9% vs. 14.8%) were higher in the SAH-COVID cohort than in controls. [62] In another cohort study that included data from 62 health care facilities using the Cerner de-identified COVID-19 dataset, there were n= 86 (0.1%) and n=376 (0.2%) patients with SAH among 85,645 patients with COVID-19 and 197,073 patients without COVID-19, respectively. The authors found that there was no increase in the risk of SAH in COVID19 patients but higher mortality probably driven by systemic complications (31.4% vs. 12.2%).[63]

Cerebral Sinus Venous Thrombosis (CSVT): In a case series from New York city at the height of the COVID-19 pandemic's first wave (March through May 2020) CSVT was diagnosed in 12 of 13,500, for a frequency of 0.088 per million as compared CSVT in the general population is 5 per million annually. [64]
In a systematic review n=34,331 COVID19 patients, the estimated frequency of CVT was 0.08 percent.[65] The superior sagittal and transverse sinuses were the most common sites for acute CVST. [66] CSVT and Vaccine Induced Thrombocytopenia (VITT) are discussed later in this review.[67]
Extracorporeal membrane oxygenation (ECMO) and neurological complications: In a systematic review on neurological complications in ECMO for COVID19 patients that included n=1,322 patients from case series and retrospective cohort studies, the prevalence of intracranial hemorrhage (ICH), ischemic

stroke, and hypoxic ischemic brain injury (HIBI) was 5.9% (n=78), 1.1% (n=15), and 0.3% (n=4), respectively. The overall mortality of the 1,296 ECMO patients in the 10 studies that reported death was 36% (n=477), and the mortality of the subset of patients who had a neurological event was 92%. [68]

In a multicenter case-control study of ECMO patients, the authors included 29/142 (20%) patients with ICH versus 4/68 (6%) non-COVID19 patients with ICH on ECMO. Half of the COVID19 patients had a clinically significant ICH and a third of them suffered in-hospital mortality. The overall ICU mortality in the presence of ICH of any severity was 88%. This study showed a six-fold increased adjusted risk for ICH and a 3.5-fold increased incidence of ICH in COVID-19 patients on ECMO, versus non-COVID19 patients.[69] In another study that included ARDS patients on ECMO comparing COVID19 versus non-COVID19 patients, ICH was detected 10% of patients with ARDS. Despite statistically higher rates of antiplatelet therapy and therapeutic anticoagulation in COVID-19 patients, a similar rate of ICH in patients with ARDS due to COVID-19 compared to other causes of ARDS. [70]

Delirium/Encephalopathy: In a systematic review that included n=48 studies with 11,553 COVID-19 patients from 13 countries, the pooled prevalence, incidence and mortality rates for delirium in COVID-19 patients were 24.3%, 32.4% and 44.5% respectively.[71]

In a hospitalized cohort of COVID19 patients n=419, about 80% of them were diagnosed with a neurological complication anytime from presentation to later during their hospitalization and 30% of these patients had encephalopathy[72] In addition, these patients often require longer ventilation with prolonged sedation and paralysis than used in many common ICU conditions

In a cohort study that included patients with severe COVID19, 84% patients were found to have neurological symptoms, mainly delirium. [73]
In a subsequent study (n=140 patients), 70% developed agitation during ICU stay. In addition, over half (17/28) of the patients had MRI abnormalities and over half (18/28) had an inflammatory CSF profile. EEG showed only non-specific findings.[74]

Delirium was present in 55% patients in the COVID-D cohort study of n=2088 critically ill COVID19 patients. Mechanical ventilation, use of restraints, and benzodiazepine, opioid, and vasopressor infusions, and antipsychotics were each associated with a higher risk of delirium the next day, whereas family visitation (in person or virtual) was associated with a lower risk of delirium.[19]

Coma/Encephalitis:

Among COVID19 patients with a disorder of consciousness (DoC), coma, serum inflammatory markers were higher as compared to COVID19 patients without coma. [75]After cessation of sedatives, patients with severe respiratory failure secondary to COVID-19 may have a prolonged period of unconsciousness which may be weeks before complete recovery. [76] In a prospective, longitudinal study, consecutive critically ill patients with COVID-19 with a DoC unexplained by sedation or structural brain injury, who underwent a brain MRI were enrolled. In additional to structural imaging, the authors performed a resting state functional MRI and diffusion MRI to evaluate functional and structural connectivity, as compared to healthy controls and patients with DoC resulting from severe traumatic brain injury (TBI). Of the twelve patients included in this study, one died shortly after enrollment and the rest recovered consciousness between 0-25 days after stopping all sedatives. [77] Given the long length of recovery time seen, caution is advised when prognosticating in these patients.

Post Intensive Care syndrome (PICS) and **Post Acute Sequelae of COVID19 (PASC)**

PICS has been described as the unintended consequences of critical care with new or worsening impairments in the physical, cognitive or mental health domains.[78]

In a single-center, observational cohort study, 294 of 622 including both COVID19 and non-COVID19 patients (median age 64 years, 36% female); 16% and 13% of these patients reported probable PTSD, 29% and 20% probable anxiety, and 32% and 24% probable depression at one and three months after hospital discharge, respectively. The authors found a similar risk of neuropsychiatric consequences in both COVID19 and non-COVID19 hospitalized patients concluding that there is a need for long-term follow-up for hospitalized patients during this pandemic should focus on the needs of both these cohorts. 72

90% of COVID19 survivors suffered from impairments one or more PICS domains in a prospective cohort from NYC. (Dangayach 2021) [80]At 3 months of follow-up, 87.5% (28/32) had not regained their baseline level of daily activities in a cohort study of COVID19 ICU survivors and 40% patients had impairments in multiple domains. [81]

Similar problems can be seen in all those who require critical care. Post intensive care syndrome (PICS) is a common constellation of physical, psychological and cognitive problems experienced by those who have been in critical care, with holistic rehabilitation programs required for each component.[82]

Patients and caregivers should be educated to monitor for persistent symptoms (Figure 3) and followed up in a multidisciplinary fashion to address the needs of patients with PASC. Dedicated COVID19 centers may not be widely available in all countries, however awareness of such centers, along with the ability to follow-up via telehealth may have help bridge the gap in meeting the needs of COVID19 survivors. Studies have shown that about half of the patients with COVID19 will develop PASC.[83] Similar to acute COVID19, PASC could also include multi-system manifestations. Recognizing that COVID19 survivors will have multi-system needs, COVID19 survivors need to be followed up in multidisciplinary clinics. For critical care survivors, impairments in different domains (physical, cognitive, behavioral) have long been characterized as post intensive care syndrome (PICS). Clinics developed for survivors of critical illness, offer a model to address PASC survivorship for both acute and non-hospitalized patients with COVID-19 for better understanding the trajectory, clustering of symptom as well as provide an opportunity to pool data to inform survivorship trajectories. A multidisciplinary program of care should include access to rehabilitation services, social work and welfare support, pharmacy, subspecialty care via direct inclusion or targeted referrals, and structured peer support program with trained moderators; coordination with primary care is essential.76

PASC clinics also offer research opportunities that should be harnessed to inform knowledge of survivorship trajectories after SARS-CoV-2 infection, and to improve service innovation and delivery. [84] While resources for follow-up and rehabilitation will vary between and within countries awareness and innovations like telehealth may help bridge the gap in meeting the needs of COVID19 survivors. Symptom assessment could be performed between 4-6 and at 12 weeks post discharge, along with screening for neuropsychiatric symptoms in addition to follow-up for other organ system involvement eg. Pulmonary, hematological, along with early referral for ongoing clinical trials, physical, occupational and cognitive therapy. [85]

Neurological complications of vaccines

There are several approved COVID19 vaccines being used in different parts of the world. Different systems are used in different parts of the world to track and report adverse events due to vaccines for eg, in the United States, the vaccine adverse events reporting systems (VAERS), In the United Kingdom, Coronavirus Yellow Card reporting website (https://coronavirus-yellowcard.mhra.gov.uk/).

Any patient or healthcare provider can report side effects of vaccines through the Centers for Disease Control (CDC) through VAERS; patients, providers, and manufacturers can also report complications to the FDA Adverse Event Reporting System (FAERS). The most common neurological symptoms included dizziness, headache, pain, muscle spasms, myalgia, and paresthesias, which are expected to occur as acute, transient effects of the vaccination. Rare cases of tremor, diplopia, tinnitus, dysphonia, seizures, and reactivation of herpes zoster have been reported. In order of reporting frequency in 2021 there are facial palsy, GBS, stroke, transverse myelitis, and acute disseminated encephalomyelitis in the VAERS database. [86] Transient episodes of headaches, myalgias, fatigue were reported in about 5% of participants in clinical trials. [87]

From the UK, in a self-controlled case series study to investigate hospital admissions from neurological complications in the 28 days after a first dose of ChAdOx1nCoV-19 (AstraZeneca) (n = 20,417,752) or BNT162b2 (Pfizer) (n = 12,134,782), and after a SARS-CoV-2-positive test (n = 2,005,280), there was an increased risk of Guillain-Barre syndrome (incidence rate ratio (IRR), 2.90 at 15-21 days after vaccination) and Bell's palsy (IRR, 1.29 at 15-21 days) with the AstraZeneca vaccine. [88]

There was an increased risk of hemorrhagic stroke (IRR, 1.38 at 15-21 days) with Pfizer vaccine. Another independent Scottish cohort provided further support for the association between the AstraZeneca vaccine and GBS (IRR, 2.32 at 1-28 days). There was a substantially higher risk of all neurological outcomes in the 28 days after a positive SARS-CoV-2 test including Guillain-Barre syndrome (IRR, 5.25). [88]

CSVT and Vaccine induced thrombocytopenia: The initial 12 US cases of CVST with thrombocytopenia after Ad26.COV2.S vaccination were reported as serious events.[89] In the UK, up to 12 January 2022, the Medicines and Healthcare products regulatory agency (MHRA) had received Yellow Card reports of 435 cases of major thromboembolic events with concurrent thrombocytopenia following vaccination with COVID-19 Vaccine AstraZeneca. Forty-nine of the 435 reports have been reported after a second dose. Of the 435 reports, 217 occurred in females, and 214 occurred in males aged from 18 to 93 years. The overall case fatality rate was 18% with 76 deaths, six of which occurred after the second dose. CSVT was reported in 157 cases (average age 46 years) and 278 had other major thromboembolic events (average age 54 years) with concurrent thrombocytopenia. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered in the UK by 12 January was 24.9 million and the estimated number of second doses was 24.2 million. There is some evidence that the reported incidence rate is higher in females compared to men although this is not seen across all age groups and the difference remains small. The overall incidence of thromboembolic events with concurrent low platelets after second doses was 2.0 cases per million doses. Considering the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicates that there is a lower reported incidence rate in younger adult age groups following the second dose compared to the older groups (1.0 per million doses in those aged 18-49 years compared to 2.1 per million doses in those aged 50 years and over). The scientific review concluded that there is a possible link between CVST without low platelets and COVID-19 Vaccine AstraZeneca.

Current advice from the US and UK governmental agencies, CDC and MHRA respectively has been that the benefit of the vaccination outweighs the risk and this appears to be accurate from a neurological standpoint. In order to establish causality, clinical case definitions must be established, for e.g. via the Brighton collaboration guidelines for conditions recognized to be associated with vaccination and proactive clinician-led definitions in emergent conditions (such as VITT). In assessing causality, tools such as the WHO GACVS or Bradford Hill criteria [90]may be used; however, we additionally propose criteria that classify associated neurological or neuropsychiatric events into probable, possible and unlikely cases, considering the temporal relationship, individual risk factors and the likelihood of an alternative etiology.

In such cases as the urgent SARS-CoV-2 vaccination campaign in which ongoing RCTs may be unfeasible and/or unethical, epidemiological methods of causality assessment such as triangulation may be used. Matt Butler 2021.[90]

Conclusion:

Neurological manifestation of acute COVID19 and PASC are common in hospitalized patients with COVID19. Having a high clinical suspicion to screen, diagnose and treat life-threatening neurological complications (such as acute ischemic stroke or intracerebral hemorrhage) are needed to help frontline providers leverage existing resources appropriately. Systems of healthcare delivery need to be optimized to prepare for the long term needs of COVID19 survivors with periodic screening for neuropsychiatric manifestations and providing multidisciplinary support to help rehabilitate these patients. Adapting existing systems to help uphold the paradigm that time is brain, address barriers for implementing evidence-based bundles for liberation from the ICU can help prevent and treat acute neurological complications and perhaps, may help reduce the burden of PASC in ICU survivors.
Patients with mild COVID19 also remain at risk of PASC. Educating these patients to self-monitor their symptoms, increasing awareness about local multidisciplinary COVID19 centers, engaging primary care can help patients with PASC return to their baseline.

Clinics Care Points

- While patients with any severity of COVID19 can suffer from neurological complications, the incidence of these complications is much higher in patients with severe COVID19. Early diagnosis of neurological complications in COVID19 patients will rely on focused bedside neurological examinations. Such focused clinical examinations can then guide a judicious utilization of imaging and electrophysiological studies. Stroke occurs in about 1.5% of all COVID19 patients and these stroke patients were younger, tend to be males, and have an increased stroke severity and worse outcomes compared with stroke patients in the pre-pandemic period.

- Hemorrhagic stroke may be seen in COVID19 patients on therapeutic anticoagulation, on ECMO or spontaneously. The pattern of ICH in these patients had different characteristics compared to ICH not associated with COVID-19, including frequent lobar location (67%) and multifocality (36%), a high rate of anticoagulation, and high mortality.

- Status epilepticus, new onset seizures, encephalitis occur rarely in COVID19 patients.

- Delirium may be present in more than half the patients with severe COVID19. There are several challenges to the implementation of the evidence-based ICU liberation in these patients including. Mechanical ventilation, use of restraints, and benzodiazepine, opioid, and vasopressor infusions, and antipsychotics, limitations on family visitation have been associated with a higher risk of delirium.

- Patients and caregivers should be educated to monitor for persistent symptoms and followed up in a multidisciplinary fashion to address the needs of patients with post-acute sequelae of COVID19 (PASC). Systems of healthcare delivery need to be optimized to prepare for the long-term needs of COVID19 survivors with periodic screening for neuropsychiatric manifestations and providing multidisciplinary support to help rehabilitate these patients.

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FIGURE LEGENDS

Figure 1. Potential mechanisms and complications of NeuroCOVID (*From* Newcombe VFJ, Dangayach NS, Sonneville R. Neurological complications of COVID-19. Intensive Care Med. 2021;47(9):1021-1023. doi:10.1007/s00134-021-06439-6; with permission)

Figure 2. Classifying neurological complications of COVID19

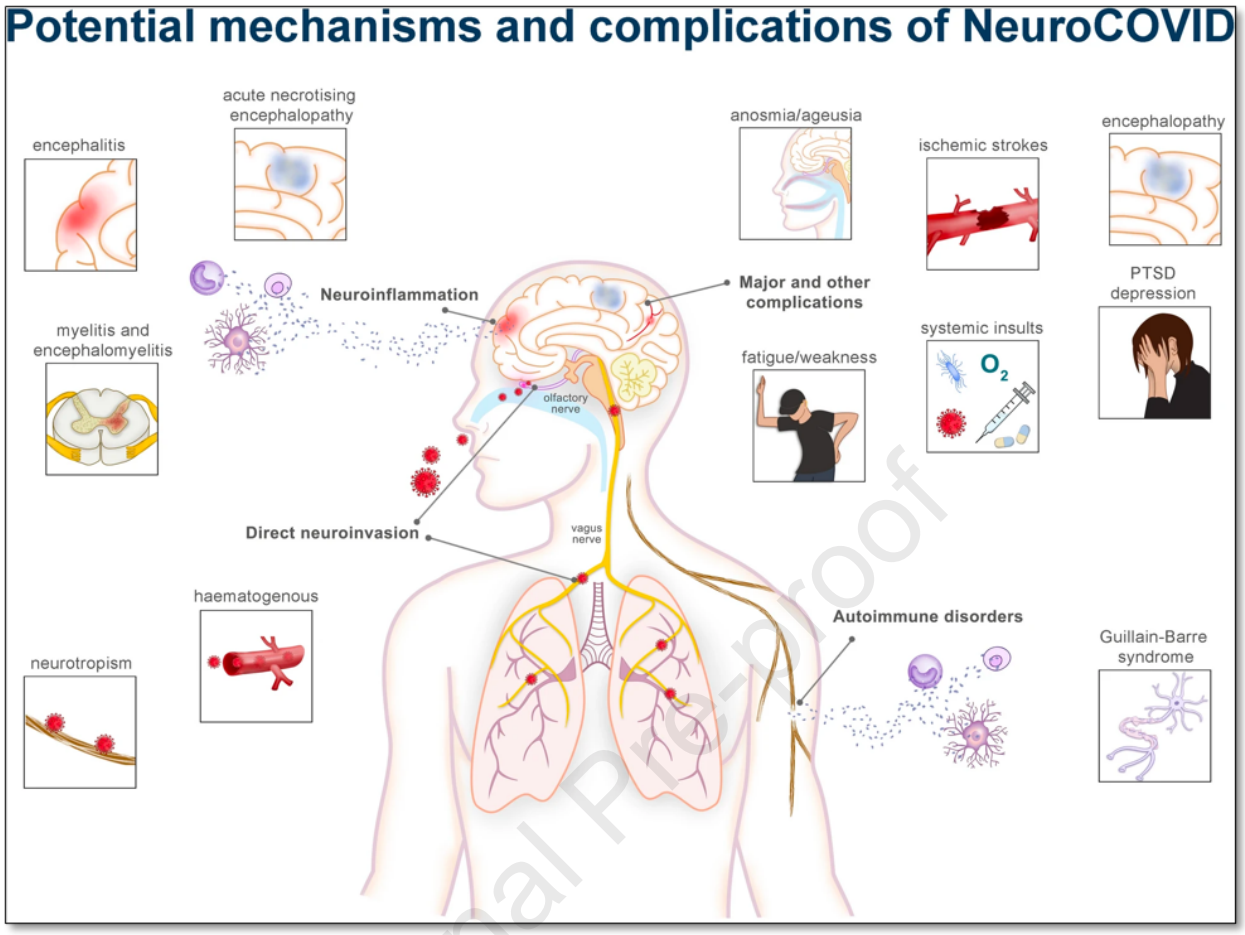
Figure 3. Common PASC symptoms (*From* Newcombe VFJ, Dangayach NS, Sonneville R. Neurological complications of COVID-19. Intensive Care Med. 2021;47(9):1021-1023. doi:10.1007/s00134-021-06439-6; with permission)

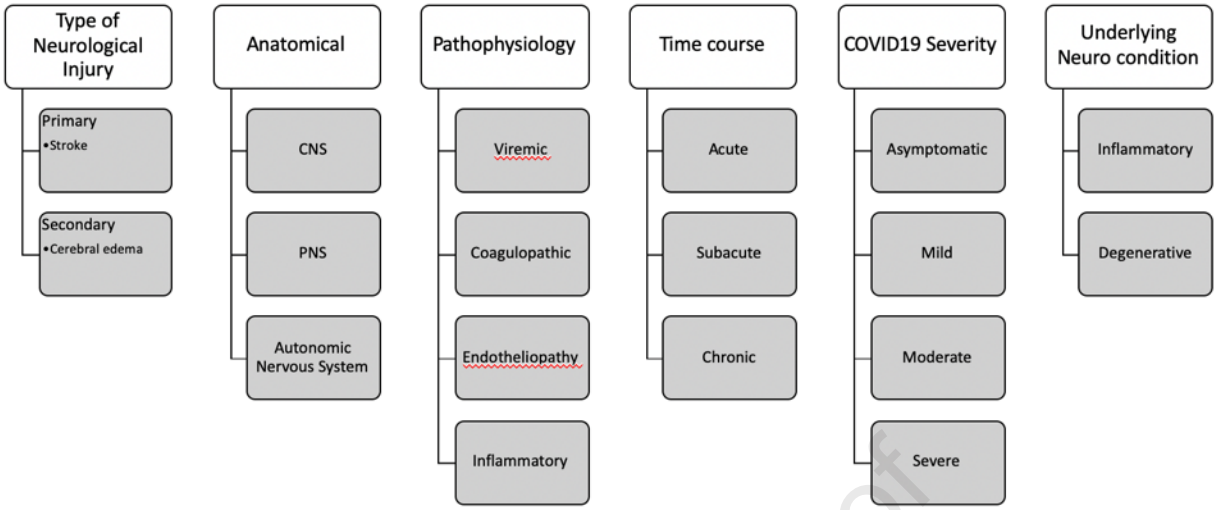
Study	Varatharaj et al[7]	Meppiel et al[8]	Frontera et al[10]	Chou et al[11]
N patients with neurologic complications	153	222	606	2439/3054
Encephalopathy	23%	30%	51%	51%
Stroke	62%	26% (ischemic strokes)	14%	3%
Seizures / status epilepticus	Not reported	9.5%	12%	1%
Acute inflammatory central nervous system syndromes*	9%	9.5%	0%	1%
PNS disease	5%	6.8%	Not reported	6%
Other	Neuropsychiatric disorders 23/125 patients	Not reported	Hypoxic brain injury 11%	Coma 17%

Table 1. Summary of Neurological manifestations in cohort studies

Mechanism/Etiology	Example
Direct viral invasion into the CNS	• Infectious encephalitis, meningitis, myelitis.
Para-infectious, immune-mediated	• ADEM • transverse myelitis • Guillain-Barré syndrome
Neurological complications of systemic disease	• Hypercoagulability -> ischemic stroke • Hypoxic respiratory failure -> hypoxic brain injury • Sepsis -> Encephalopathy/delirium
Exacerbation of baseline neurological disorder	• Epilepsy: increased seizure frequency/status epilepticus • Multiple sclerosis flare
Treatment-associated neurological complications	• Anticoagulation -> CNS hemorrhages • Steroids & paralytic medications -> critical illness neuropathy / myopathy • Sedatives -> delirium / encephalopathy
Thrombotic complications	• Stroke: arterial and venous
Associated with Critical illness	• Post Intensive Care Syndrome
Unclear	• Long-COVID

Table 2. Mechanism of injury and clinical examples of neurological complications





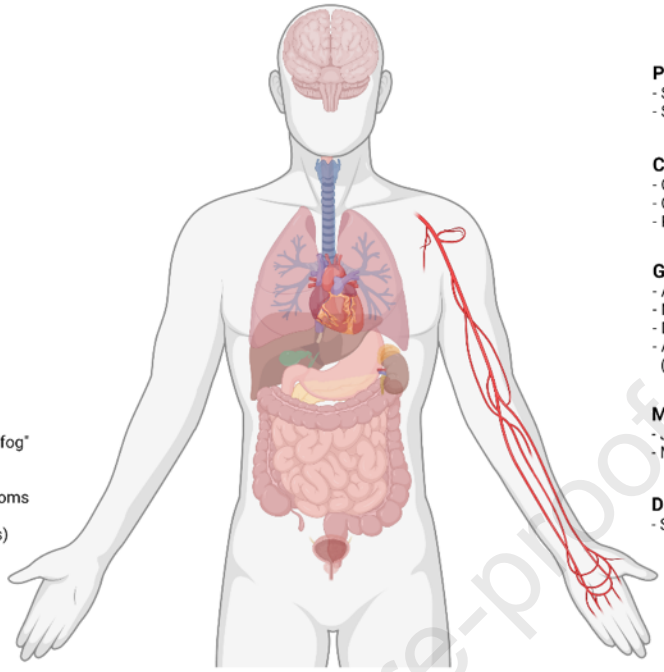
Common PASC / long COVID symptoms

Ear, nose and throat
- Tinnitus
- Earache
- Sore throat
- Dizziness
- Loss of taste and/or smell

Respiratory
- Breathlessness
- Cough

Generalised
- Fatigue
- Fever
- Pain

Neurological
- Cognitive impairment ("brain fog"
- Headache
- Sleep dirturbance
- Peripheral neuropathy symptoms
- Dizziness
- Delirium (in older populations)



Psychological/psychiatric
- Symptoms of depression
- Symptoms of anxiety

Cardiovascular
- Chest tightness
- Chest pain
- Palpitations

Gastrointenstinal
- Abdominal pain
- Nausea
- Diarrhoea
- Anorexia and reduced appetite (in older populations)

Musculoskeletal
- Joint pain
- Muscle pain

Dermatological
- Skin rashes